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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,026	08/18/2006	Nobuhiro Oikawa	OIKAWA1	5830

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BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
04/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,026	OIKAWA ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments filed 01/14/2009 were entered.

Response to Arguments

2. Applicants' arguments, filed 01/14/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Election/Restrictions

3. In the Requirement for Restriction mailed on 07/24/2008, Applicant was required to elect a single compound species of Formula (1). This requirement has been withdrawn. Accordingly, all claims encompassed by elected Group I, including claims drawn to non-elected compound specie, are hereby rejoined.

4. It is noted, however, that Applicant has amended claim 1 to limit the definition of Y^1. In doing so, claim 1 and all claims that depend on claim 1, no longer encompass the originally elected species Compound 152.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3 and 6-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some of the compound encompassed by the claims, does not reasonably provide enablement for all of the compounds encompassed by the claims. Specifically, the specification does not enable any person skilled in the art to make and use the invention wherein R^3 and R^4 are given their **full** scope as recited by instant claim 1. Applicant **is** enabled for compound wherein R^3 and R^4 are independently selected from a hydrogen atom, a halogen atom, -NRfRg, -CONRfRg, a C_1-C_6 alkyl group, C_1-C_6 alkoxy group, and –T-$(CH_2)_k$-V. However, Applicant is **not** enabled for a compound wherein R^3 or R^4 is –CH=NORe. Furthermore, Applicant is not enabled for a compound wherein R^3 or R^4 is –T-$(CH_2)_k$-V **and** V is substituted by one or more Y^3. Additionally, Applicant is not enabled for a compound wherein W is substituted by one or more Y^3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

7. Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered, with the most relevant factors discussed below.

8. Nature of the invention: The invention is drawn to compounds which are alleged to be Raf inhibitors useful in the treatment of cancer, psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetes. It is well know and one of ordinary skill in the art

would recognize that the development of specific kinase inhibitors is a complicated and complex undertaking.

9. Breadth of the claims: The claims, which recite a generic compound of formula (1) containing a number of variable groups, many of which contain additional variables, encompass literally millions of potential compounds. In particular, instant claim 1 recites that R^3 and R^4 are can be –CH=NORe as well as –T-$(CH_2)_k$-V **wherein** V is substituted by one or more Y^3. Furthermore, Y^3 is defined to include –NRaRb, CONRaRb, -OC(=O)NRa'Rb', etc. As such, the broad definition of R^3 and R^4, which includes –CH=NORe and, moreover, –T-$(CH_2)_k$-V **wherein** V is substituted by one or more Y^3, encompasses literally millions of potential compounds. Furthermore, since W can also be substituted by one or more Y^3, additional compounds are encompassed by the claims. Accordingly, the claims are broad. Moreover, the broadness of the claims exacerbates the complexity of the invention in that they require that the millions of distinct compound species encompassed by the full scope of R^3, R^4, and W would function as Raf inhibitors.

10. Guidance of the specification/The existence of working examples: The specification provides evidence that 29 compounds possess Raf inhibitor activity, 23 of which are within the elected Group I. However, none of the 29 compounds contain R^3 or R^4 which is –CH=NORe. Furthermore, none of the 29 compounds contain R^3 or R^4 which is –T-$(CH_2)_k$-V **and** V is substituted by one or more Y^3 (i.e., although the specification discloses compounds having Raf inhibitory activity wherein R^3 or R^4 is –T-$(CH_2)_k$-V, there is no disclosure of compounds wherein V is substituted by one or more

Y^3 as having Raf inhibitory activity). And none of the 29 compounds contain W wherein W is substituted by one or more Y^3 (i.e., the specification discloses compounds wherein W is NRaRb (21 of the 29 compounds), N(Ra)C(=O)NRa'Rb' (3 of the 29 compounds), N=C(Rc)NRaRb (1 of the 29 compounds); however none of the compounds are futher substituted with one to three substituents selected from Y3 as encompassed by the claims). Thus, of the millions of potential compounds encompassed by R^3, R^4 and W as defined, Applicant has disclosed 29 such compounds which possess Raf inhibitory activity, and none wherein R^3 or R^4 is –CH=NORe or $-T-(CH_2)_k-V$ **wherein** V is substituted by one or more Y^3 or wherein W is substituted by one to three Y^3.

11. State of the art/Predictability of the art: Urea compounds useful as Raf inhibitors are well known in the art. However, it is also well known in the art that minor structural changes to these compounds will have a significant impact on the Raf inhibitory activity of each compound. As evidenced by *Khire et al* (Biorg Med Chem Lett 14:783-786, 2004; cited in a previous Action) a shift from hydrogen to methyl in a terminal substituent in a urea Raf kinase inhibitor altered the Raf kinase IC50 $(nM)^9$ from 120 to 5800 (Page 784, Table I, compare Compound 2 with Compound 8). Accordingly, it would be impossible for one of ordinary skill in the art at the time the invention was made to reasonably predict which of the millions of compounds encompassed by the variable R^3, R^4 and W groups possess anti-Raf activity. The person of ordinary skill in the art would be required to make and test each of the compounds to determine which, if any, possess such activity.

12. Amount of experimentation necessary: In light of the complexity of the invention, coupled with the broadness of the claims which exacerbate the complexity, and further in light of the lack of guidance and unpredictability of the art, it would require undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 103

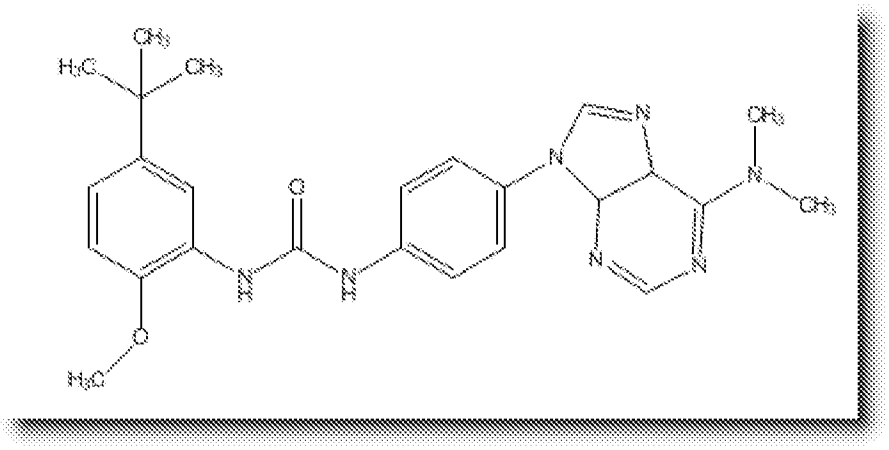
13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

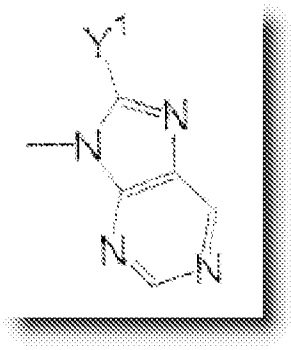
14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. **Claims 1 and 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Cirillo et al* (WO 2003/032989) in view of *Miller et al* (WO 1999/32436).**

16. Instant claim 1 is drawn to compounds of formula (1) which encompass the following compound species:

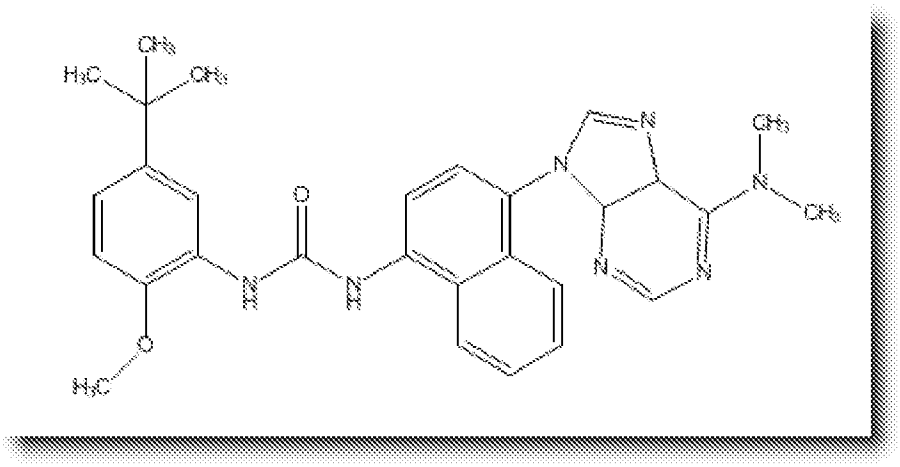


wherein R^1, R^3 and R^4 are hydrogen; R^2 is a C_1-C_6 alkyl group and R^5 is a C_1-C_6 alkoxy group; Z^1 and Z^2 are hydrogen; R^6 and R^7 are hydrogen; Q is



optionally substituted with W wherein W is –NRaRb (and Ra and Rb are a C_1-C_{10} alkyl) and wherein Y^1 (in Q) is hydrogen, which reads upon claims 1 and 7.

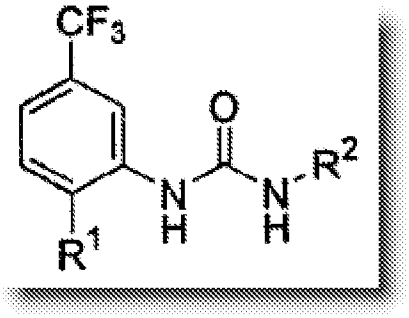
17. *Cirillo et al* teach the following structurally related compound



(The second compound listed on Page 36). Notably, the only difference between the compound taught by *Cirillo et al* and the compound of instant claims 1 and 7 is the substitution of naphthyl (as taught by *Cirillo et al*) for phenyl (as recited by the instant claims). It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to substitute naphthyl (as taught by *Cirillo et al*) with phenyl for the following reasons:

18. **FIRST**, it is well known in the art and would have been obvious to a person of ordinary skill in the art at the time the invention was made that phenyl and naphthyl are bioisosteres that can be easily substituted.

19. **SECOND**, *Miller et al* teach structurally related urea compounds



where R^2 can be either phenyl **or** naphthyl (See, for example, Page 64, Table 2, compare Examples 27 and 28). Accordingly, *Miller et al* teach that structurally related urea compounds having **either naphthyl or phenyl** at the specific point of distinction between *Cirillo et al* and the instant compound species are alternatively usable.

20. As stated by the court in *Aventis Pharma Deutschland GMBH and King Pharmaceuticals, Inc. v Lupin, Ltd.*, No 06-1530 (Fed. Cir. 2007), "[i]n the chemical arts, we have long head that 'structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima face* case of obviousness'" citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, No 06-1329 (Fed. Cir. 2007) (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990)). And, furthermore, that "[t]he 'reason or motivation' need not be an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship... to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old" citing *Dillon* at 692. "Once such a *prima facie* case is

established, it falls to the applicant or patentee to rebut it…" citing *Dillon* at 692. In the instant case, the claimed and prior art compounds are structurally similar, differing in that the compounds taught by the prior art contain a naphthyl group where as the compounds of the instant invention contain a phenyl group. However, a person of ordinary skill in the art at the time the invention was made would have found it obvious to replace naphthyl (in the compounds taught by *Cirillo et al*) with phenyl (as taught by the instant application) in light of the fact that phenyl and naphthyl are well known bioisosteres that can be easily substituted (i.e., phenyl and naphthyl are well known functional equivalents) and further in light of *Miller et al* which specifically teach structurally related compounds having either naphthyl **or** phenyl are functionally equivalent and are thus either group is alternatively useable, and the skilled artisan would have reasonably expected the new compound to possess similar properties to the old compound.

21. Instant claim 9 is drawn to "a pharmaceutical composition comprising a compound… of claim 1 as an active ingredient" (claim 9). *Cirillo et al* specifically teach that "Compounds of the invention may be physically combined with the conventional therapeutics or other adjuvants into a single pharmaceutical composition" (Page 44, Lines 24-26).

22. Instant claims 8 and 10-11 are drawn to the compound of claim 1 which "has Raf inhibiting effect and angiogenesis inhibiting effect and is used for treating… atherosclerosis" etc (claim 8); is a "raf inhibitor or an angiogenesis inhibitor" (claim 10); and is a "therapeutic agent for a disease selected from… atherosclerosis" etc (claim

11). Applicant is advised that such intended use limitations within product claims do not carry patentable weight. As stated by MPEP 2111.02:

> If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999).

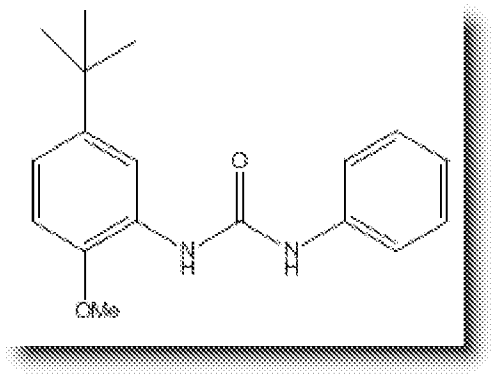
The body of instant claims 8 and 10-11, which are drawn to compositions comprising the compound of instant claim 1 as an active ingredient, clearly set forth all of the limitations of the claimed invention. Accordingly, the purpose and intended uses recited by the claims carry no patentable weight. Claims 8 and 10-11 are thus *prima facie* obvious for the same reasons as applied to instant claim 9 above. Furthermore, *assuming arguendo* that such use limitations did carry patentable weight, absent evidence to the contrary, it is asserted that the *prima facie* obvious compound taught above would necessarily function as a Raf inhibitor and an angiogenesis inhibitor useful for the treatment of atherosclerosis. Indeed, *Cirillo et al* specifically teach that the compounds are useful for the treatment of atherosclerosis (Page 43, Line 9) and the structurally similar compounds taught by *Miller et al* relates to the use of a group of aryl ureas in treating raf mediated diseases and pharmaceutical compositions for use in such therapy" (Page 1, Lines 12-13); more specifically, "compounds which are inhibitors of the enzyme raf kinase" (Page 2, Lines 6-7). "Where... the claimed and prior art products are identical or substantially

identical... the PTO can require an applicant to prove that the prior art products do not necessarily or inherently posses the characteristics of his claimed product. Whether the rejected is based on 'inherency' under 35 USC 102, on '*prima facie* obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products" *In re Best, Boiton, and Shaw* 195 USPQ 430, 433, 562 F2d 1252 (CCPA 1977).

23. **Claims 2-3 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Cirillo et al* (WO 2003/032989) in view of *Miller et al* (WO 1999/32436) as applied to claim 1 above, in further view of *Curtin et al* (Bioorg Med Chem Lett 14:4505-4509, 2004).**

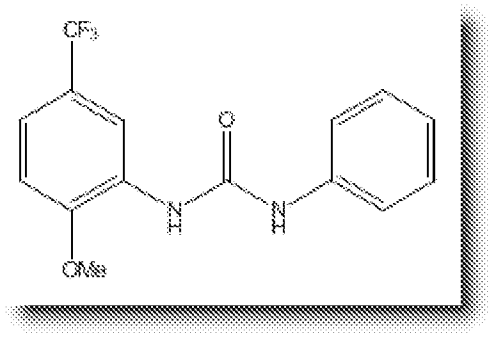
24. Instant claims 2-3 and 6 are drawn to the compound of claim 1 wherein R^2 is halogen, a trifluoromethyl group or a triluromethoxy group (claims 2-3) or wherein R^1-R^5 are each independently selected from a hydrogen atom, a chlorine atom, a fluorine atom, a bromine atom and a trilfluoromethyl group (claim 6). As discussed above, *Cirillo et al* in view of *Miller et al* teach compounds of instant claim 1. Furthermore,

Miller et al teach compounds having each of the following cores:



(Page 62, Table I)

and



(Page 64, Table 2).

25. Additionally, *Curtin et al* teach structurally related kinase inhibitors wherein R^1-R^5 on the terminal phenyl are each selected from a hydrogen atom, a chlorine atom, a fluorine atom, a trifluoromethyl group and a C1-C3 alkyl or alkoxy group. As evidenced by *Curtin et al*, trifluoromethyl and hydrogen are significantly more active as kinase inhibitors than alkoxy and hydrogen (Page 4507, Table 2, compare Compound 4e with Compound 4j).

26. Accordingly, one of ordinary skill in the art would have been motivated to substitute the terminal phenyl substituents taught by *Cirillo et al* (which teach compounds having alkoxy and alkyl substituents) with trifluoromethyl in view of *Miller et*

al which specifically teach structurally related compounds having either substitution are functionally equivalent and are thus either group is alternatively useable in phenyl urea compounds. The simple substitution of one known element for another to obtain predictable results is *prima facie* obvious. Furthermore, a person of ordinary skill in the art at the time the invention was made would have been motivated to make compounds encompassed by instant claims 2-3 and 6 as taught by *Curtin et al* (Page 4507, Table 2, Compound 4e and 4o) since the recited substituents provided increased kinase inhibitory activity when compared to compounds containing alkyl or alkoxy substituents. Accordingly, the skilled artisan would have been motivated to make the substitutions encompassed by instant claims 2-3 and 6 in an effort to increase the activity of the compounds and with a reasonable expectation of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614